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Kimberly O. Snead

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#11
Appeal Brief
S. Bryce
12/2/03

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re:

SCHULER et al. Atty. Docket No. GC-425

Application No. 09/811,754 ✓ Examiner: Maynard, J.

Filing Date: March 19, 2001 Art Unit: 3763

Title: USE OF STREPTOMYCES HYALUROLYTICUS ENZYME IN OPHTHALMIC TREATMENTS

Commissioner for Patents
Mail Stop Appeal Brief—Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPEAL BRIEF IN TRIPLICATE UNDER 37 CFR 1.192

Dear Sir:

Pursuant to the Final Office Action, dated May 12, 2003, the Advisory Action dated August 8, 2003, and the Notice of Appeal dated September 12, 2003, for the above-identified patent application, the following timely Appeal Brief in triplicate is respectfully submitted. Please charge any deficiency in fees to Deposit Account No. 16-0478.

AUTHORITIES

References

Fini, M. Elizabeth, www.bpei.med.miami.edu/site/current/researchbio.asp?bio-fini, ©1997-2003.
Johnson, Mark, Aqueous Humor Outflow Resistance (Iser Debate), www.glaucom.com/meetings/4-3/iser.htm, 2002.

Cases

In re Fine, 837 F.2d 1071, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988).
In re Geisler, 116 F.3d 1465, 43 U.S.P.Q.2d 1362 (Fed. Cir. 1977).
In re Jones, 958 F.2d 347, 21 U.S.P.Q.2d 1941 (Fed. Cir. 1992).
In re Merck & Co., Inc., 800 F.2d 1091, 231 U.S.P.Q.2d 375 (Fed. Cir. 1986).
In re Royka, 490 F.2d 981, 180 U.S.P.Q. 580 (CCPA 1974).
In re Vaeck, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

Real Party in Interest

Christopher Schuler, having a principal residence at 9117 Three Notch Road, Troy, Virginia 22974 and Ed Schuler, having a principal residence at 9117 Three Notch Road, Troy, Virginia 22974, being the inventors, are the Real Parties in Interest.

1. Related Appeals and Interferences

No other appeals or interferences are known to appellant, appellant's legal representative, or assignee that will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

2. Status of Claims

Claims 1 and 3-9 are pending, and Claim 2 has been cancelled. Claims 1, 3, 5, and 7-9 stand rejected. Claims 4 and 6 are allowed. The rejection of Claims 1, 3, 5, and 7-9 is hereby appealed. Appendix A contains a list of pending claims.

3. Status of Amendments

The proposed amendments provided in the Response to Final Office Action, dated July 14, 2003, were entered. The rejection of claims 4 and 6 under 35 USC 103(a) regarding the obviousness of using hyaluronidase to soften the cornea of an eye and using hyaluronidase to make artificial lenses have been withdrawn. The rejections of Claim 1-3, 5, and 7-9 under 35 USC 103(a) remain.

4. Summary of Invention

The instant invention is directed to the use of an alternative source of hyaluronidase, purified from the bacteria *Streptomyces hyalurolyticus*, for the treatment of ophthalmic disorders. See, for example, the "Summary of Invention" at page 3, lines 20-23, and page 4, lines 1-18, of the application.

5. Issues

Whether Claim 1, drawn to a method for accelerating the clearance of hemorrhagic blood from the vitreous humor of a mammalian eye, comprising the step of injecting into the vitreous humor a solution which contains hyaluronidase from *Streptomyces hyalurolyticus* to provide a dose having a hyaluronidase activity of at least about 10 Turbidity Reducing Units (TRU) of said hyaluronidase, said solution being essentially free of contaminating protease is unpatentable under 35 USC 103(a) for obviousness based on the disclosure of Karageozian (WO 00/66139) in view of Knepper et al. (Invest Ophthalmol Vis Sci 1984), and further in view of Yasuyuki et al. (US 3728223 A).

Whether claim 3, drawn to a method of treating eye disorders comprising the step of applying essentially protease-free hyaluronidase from *Streptomyces hyalurolyticus* to the eye, wherein said hyaluronidase is dissolved in a saline solution, and wherein said treating of said eye disorders is the clearing of hemorrhagic blood from the vitreous humor of a mammalian eye using an amount of hyaluronidase sufficient to clear the blood, is unpatentable under 35 USC 103(a) for obviousness based on the disclosure of

Karageozian (WO 00/66139) in view of Knepper et al. (Invest Ophthalmol Vis Sci 1984), and further in view of Yasuyuki et al. (US 3728223 A) and Karageozian et al. (US 5866120 A).

Whether Claim 5, drawn to a method of treating eye disorders comprising the step of applying essentially protease-free hyaluronidase from *Streptomyces hyalurolyticus* to the eye, wherein said hyaluronidase is dissolved in a saline solution, and wherein said treating of an eye disorder is the spreading local anesthesia more effectively through ocular tissue prior to surgical interventions by using an amount of hyaluronidase sufficient to spread anesthesia, is unpatentable under 35 USC 103(a) for obviousness based on the disclosure of Karageozian (WO 00/66139) in view of Knepper et al. (Invest Ophthalmol Vis Sci 1984), and further in view of Yasuyuki et al. (US 3728223 A) and Straus (US 4759746 A).

Whether Claims 7-9, drawn to a method of treating eye disorders comprising the step of applying essentially protease-free hyaluronidase from *Streptomyces hyalurolyticus* to the eye, wherein said hyaluronidase is dissolved in a saline solution, and wherein said treating of an eye disorder is the stimulating of flow of physiological fluids in the eye which comprises contacting a physiological fluid of the eye with a said hyaluroinidase using an amount of hyaluronidase sufficient to stimulate the flow of said fluid, is unpatentable under 35 USC 103(a) for obviousness based on the disclosure of Karageozian (WO 00/66139) in view of Knepper et al. (Invest Ophthalmol Vis Sci 1984), and further in view of Yasuyuki et al. (US 3728223 A).

6. Grouping of Claims

The claims do not all stand or fall together. They are divided into three (3) groups as follows:

1) Claims 1 and 3, drawn to a method for accelerating the clearance of hemorrhagic blood from the vitreous humor of a mammalian eye by injecting into the vitreous humor a solution containing hyaluronidase from *Streptomyces hyalurolyticus.*

2) Claim 5, drawn to method spreading local anesthesia effectively through the ocular tissue prior to surgical interventions by applying essentially protease-free hyaluronidase from *Streptomyces hyalurolyticus* to the eye.

3) Claims 7-9, drawn to a method of stimulating of flow of physiological fluids in the eye by applying essentially protease-free hyaluronidase from *Streptomyces hyalurolyticus* to the eye.

7. Argument

The Examiner has failed to prove a prima facie case of obviousness under 35 USC 103(a) based on the disclosure of Karageozian in view of Knepper et al., and further in view of Yasuyuki et al., Karageozian et al., and Straus.

Claims 1, 3, 5, and 7-9, drawn generally to methods of treating eye disorders by applying hyaluronidase from *Streptomyces hyalurolyticus* to the eye, are patentable and are not obvious under 35 USC 103(a) based on the disclosure of Karageozian (WO 00/66139) in view of Knepper et al. (Invest Ophthalmol Vis Sci 1984),

and further in view of Yasuyuki et al. (US 3728223 A), Karageozian et al. (US 5866120 A), and Straus (US 4759746 A).

Three criteria must be met to establish a case of prima facie obviousness: 1) the references must teach or suggest all the claim limitations, 2) there must be some suggestion or motivation to modify or combine references, and 3) there must be a reasonable expectation of success. The teaching or suggestion to make the combination and the reasonable expectation of success must both be found in the cited art, not the applicant's disclosure. *In re Vaeck,* 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

A reasonable reading of the cited references indicates that, taken together, they satisfy none of the three criteria stated above.

I. Reasons for Grouping of Claims

The elected inventions are drawn to methods of treating different eye disorders, and accordingly are drawn to three distinct groups. 1) Claims 1 and 3 are drawn to a method for accelerating the clearance of hemorrhagic blood from the vitreous humor of a mammalian eye by injecting into the vitreous humor a solution containing hyaluronidase from *Streptomyces hyalurolyticus.* 2) Claim 5 is drawn to a method for spreading local anesthesia effectively through the ocular tissue prior to surgical interventions by applying essentially protease-free hyaluronidase from *Streptomyces hyalurolyticus* to the eye. 3) Claims 7-9 are drawn to methods of stimulating flow of physiological fluids in the eye by applying essentially protease-free hyaluronidase from *Streptomyces hyalurolyticus* to the eye.

The inventions do not stand or fall together. The differences between Groups 1, 2, and 3 is the eye disorder being treated by the application of hyaluronidase. Claims 1 and 3 deal with clearing hemorrhagic blood from the vitreous humor, Claim 5 deals with spreading local anesthesia, and Claims 7-9 deal with stimulating flow of physiological fluids in the eye. The differences are important because there is no indication that using hyaluronidase to treat one disorder makes it viable for use with another disorder.

II. The cited art does not teach or suggest all the claim limitations.

To establish prima facie obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (CCPA 1974).

A. Karageozian et al., Knepper et al., and Yasuyuki et al. do not teach or suggest all the claim limitations of Claims 1 and 3.

The claimed invention of claims 1 and 3 are drawn to methods of treating an eye disorder by applying a sufficient amount of protease-free hyaluronidase derived from *Streptomyces hyalurolyticus* to the eye, wherein the treating of the eye disorder is clearing of hemorrhagic blood from the vitreous humor of the eye. These claim limitations are neither taught nor suggested by the art.

1. The cited art does not teach all claim limitations.

Karageozian et al. discloses using hyaluronidase derived from the ovine testicle to accelerate the clearance of hemorrhagic blood. Knepper et al. discloses infusing rabbits' eyes with Streptomyces hyaluronidase in order to decrease aqueous outflow resistance, and Yasuyuki et al. discloses the production of hyaluronidase from Streptomyces

Hyalurolyticus. The Examiner asserts that it would have been obvious to one of ordinary skill in the art to use a purified form of hyaluronidase derived from Streptomyces hyalurolyticus as taught by Yasuyuki et al. to modify Karageozian et al.'s method of clearing hemorrhagic blood by using hyaluronidase derived from Streptomyces instead of ovine testes because Knepper discloses that Streptomyces hyaluronidase is more effective than testicular hyaluronidase in decreasing outflow resistance in the eye. Applicant respectfully disagrees with this assertion.

The Examiner acknowledges that Karageozian et al. fails to teach a method utilizing a hyaluronidase derived from Streptomyces to treat optical disorders. Knepper et al. fails to teach hyaluronidase from Streptomyces to clear hemorrhagic blood from the eye. Knepper et al. only teaches that application of hyaluronidase derived from Streptomyces to a mammalian eye is possible, but does not expressly teach benefits or uses of such application. Yusayuki et al. does not provide the teaching of Streptomyces-derived hyaluronidase to clear hemorrhagic blood from the eye, but instead merely discloses a method of producing purified hyaluronidase.

Thus, the Examiner acknowledges that Karageozian et al. does not teach the claimed invention of clearing hemorrhagic blood from the eye using Streptomyces-derived hyaluronidase, and the other cited references do not provide the failures of Karageozian et al. Accordingly, the requirement for teaching of all claim limitations of claims 1 and 3 is not met.

2. <u>The cited art does not suggest all claim limitations.</u>

In addition to not teaching all the claim limitations of Claims 1 and 3, the cited art does not suggest all the claim limitations. Moreover, the Examiner does not provide a

reasoned explanation for how the cited art taken together allegedly suggests all the claim limitations. In page 2, lines 4-7 of the Advisory Action, the Examiner simply states that "[T]he motivation to modify Karageozian et al.'s method by substituting Streptomyces hyaluronidase for Karageozian et al.'s bovine testicular hyaluronidase would be obvious as it was shown by Knepper et al. to be more effective in decreasing aqueous outflow resistance which would be pertinent to Karageozian et al., as less resistance would inherently accelerate the clearance of hemorrhagic blood by aiding in outflow of fluid away from the eye." Applicant respectfully disagrees with this assertion.

The Examiner admits that Karageozian et al. does not teach or suggest using Streptomyces-derived hyaluronidase to clear hemorrhagic blood from the eye, while Knepper et al. at most suggests that hyaluronidase decreases aqueous outflow resistance in the eye. The Examiner provides no link between decreasing aqueous outflow resistance and the clearing of hemorrhagic blood from the vitreous humor of the eye. The eye has an aqueous outflow pathway that serves to drain the eye. *Fini, M. Elizabeth*, www.bpei.med.miami.edu/site/current/researchbio.asp?bio-fini, p.1. Aqueous outflow resistance occurs when the aqueous outflow pathway fails to drain properly, thereby leading to increased intraocular pressure. *Fini*, p. 1. Aqueous outflow does not refer to the general flow of all fluids from the eye as suggested by the Examiner. After much research, those skilled in the art still do not know the cause of the majority of aqueous humor outflow resistance. *Johnson, Mark*, Aqueous Humor Outflow Resistance (Iser Debate), www.glaucom.com/meetings/4-3/iser.htm. Hemorrhagic blood is not caused by a malfunction of the aqueous outflow pathway, but instead is caused by trauma, diabetic retinopathy, or other disorders causing rupture of the retinal blood vessels. Further,

hemorrhagic blood does not naturally clear from the eye via the aqueous outflow pathway. Hemorrhagic blood clears naturally from the eye because the anterior aqueous fluid in the eye gradually absorbs the red blood cells, i.e. the blood is reabsorbed by the body. Essentially, there is no link between hemorrhagic blood in the eye and aqueous outflow resistance. Further, since those skilled in the art do not know why aqueous outflow resistance occurs, one cannot know how Streptomyces hyaluronidase reverses this resistance. Knepper et al. provides no explanation as to the effects of Streptomyces hyaluronidase, and the Examiner has provided no link between the aqueous outflow pathway and clearance of hemorrhagic blood in the eye; therefore, it would not have been obvious to one skilled in the art to modify Karageozian et al. using Knepper et al.

Thus, Karageozian et al., Knepper et al., and Yasuyuki et al. do not teach or suggest all the claim limitations of a method to clear hemorrhagic blood from the eye using Streptomyces-derived, protease-free hyaluronidase. Therefore, the Examiner has failed to make a prima facie case for obviousness, and the rejection of Claim 1 and 3 cannot stand.

B. Karageozian, Knepper et al., Yasuyuki et al., and Straus do not teach or suggest all the claim limitations of Claim 5.

The claimed invention of claim 5 is drawn to a method of treating an eye disorder by applying a sufficient amount of protease-free hyaluronidase from *Streptomyces hyalurolyticus* to the eye, wherein the treating of the eye disorder is enhancing the spread of local anesthesia through the extraocular tissue. This claim limitation is neither taught nor suggested by the art.

1. The cited art does not teach the claim limitation of claim 5.

Karageozian discloses a method for eliminating corneal collagen fiber disorganization to improve vision by applying a hyaluronidase preparation to the eye to effectively reorganize corneal collagen to rehabilitate irregularities and improve refractive errors that result from corneal surgeries.

The Examiner admits on page 4 of the final office action that "Karageozian in view of Knepper et al. and further in view of Yasuyuki et al. fail to disclose utilizing hyaluronidase to enhance spreading of local anesthesia through ocular tissue." However, the Examiner asserts that Straus discloses intraocularly injecting a local anesthetic mixture including 1cc of hyaluronidase, and, therefore, it would have been obvious to modify the method of Karageozian in view of Knepper et al. and further in view of Yasuyuki et al. by utilizing hyaluronidase to spread local anesthetic as disclosed by Straus as hyaluronidase was known to be effective in enhancing the spread of local anesthesia through ocular tissue. Applicant respectfully disagrees with this assertion.

While the Straus mixture does contain hyaluronidase, Straus does not teach using hyaluronidase derived from Streptomyces to spread local anesthesia. Accordingly, the shortcomings of Karageozian in view of Knepper et al. and further in view of Yasuyuki et al. are not taught by Straus. Accordingly, the requirement for teaching of all claim limitations is not met.

2. <u>The cited art does not suggest the claim limitations of claim 5.</u>

In addition to not teaching all the claim limitations of Claims 5, the cited art does not suggest all the claim limitations. The Examiner asserts that Straus' disclosure of injecting a local anesthetic into the eye that includes 1cc of hyaluronidase proves that hyaluronidase was known to be effective in enhancing the spread of local anesthesia, and

therefore, when combined with Karageozian, Knepper et al., and Yasuyuki et al., rendered obvious the extraocular application of Streptomyces hyaluronidase to the eye to enhance the spread of local anesthesia. Applicant respectfully disagrees with this assertion.

First, Straus does not suggest using *Streptomyces* hyaluronidase to enhance spread of local anesthetic in the eye. The Examiner admits this fact, but asserts that Knepper et al. provides the motivation for doing so. However, Knepper et al. suggests only the injection of Streptomyces hyaluronidase into the eye as a possible means for reducing aqueous outflow resistance. As explained above at page 10, lines 9-23 and page 11, lines 1-10, aqueous outflow resistance is a complicated, isolated disorder that prevents fluid from flowing through the aqueous outflow pathway out of the eye. The Examiner provides no explanation or link between aqueous outflow resistance and enhanced spreading of local anesthetic and neither Knepper et al. nor Straus suggest such a link.

Further, with regards to enhanced spreading of local anesthetic in the present invention, the Streptomyces hyaluronidase is *applied* extraocularly to the eye, while, in contrast, the Streptomyces hyaluronidase of Knepper et al. and the hyaluronidase of Straus are both *injected* intraocularly into the eye. None of the cited references, Karageozian, Knepper et al., Yasuyuki et al., nor Straus, together or in combination, suggest extraocularly applying Streptomyces hyaluronidase to the eye nor provide any suggestion or explanation as to how intraocular injection of a different form of hyaluronidase would render the present invention obvious. Accordingly, the requirement for teaching all claim limitations is not met.

C. Karageozian, Knepper et al., and Yasuyuki et al. do not do not teach or suggest all the claim limitations of Claims 7-9.

The claimed invention of claim 7-9 is drawn to a method of treating an eye disorder by applying a sufficient amount of protease-free hyaluronidase from *Streptomyces hyalurolyticus* to the eye, wherein the treating of the eye disorder is stimulating flow of physiological fluids in the eye. This claim limitation is neither taught nor suggested by the art.

Karageozian discloses using a hyaluronidase preparation to correct corneal collagen fiber disorganization, Knepper et al. discloses using Streptomyces hyaluronidase to decrease aqueous outflow resistance, and Yasuyuki et al. discloses the preparation of Streptomyces hyaluronidase.

The Examiner admits on page 2 of the final office action that "Karageozian fails to disclose a method utilizing a hyaluronidase derived from Streptomyces for intraocular therapy to treat a variety of ophthamological conditions." However, the Examiner asserts that Knepper et al. discloses that Streptomyces hyaluronidase is more effective than testicularly derived hyaluronidase in decreasing outflow resistance in the eye, therefore, it would have been obvious to modify the method of Karageozian in view of Knepper et al. and further in view of Yasuyuki et al. by utilizing Streptomyces hyaluronidase to stimulate flow of physiological fluids in the eye since Streptomyces hyaluronidase was known to decrease aqueous outflow resistance. Applicant respectfully disagrees with this assertion.

Knepper et al. does not teach or suggest using hyaluronidase derived from Streptomyces to generally stimulate flow of physiological fluids in the eye. As

previously discussed, Knepper et al. only teaches that Streptomyces hyaluronidase decreases aqueous outflow resistance, and aqueous outflow resistance is a particular disorder of the aqueous outflow pathway. Knepper et al. does not teach or suggest that decreasing aqueous outflow resistance stimulates the flow of all physiological fluids of the eye, and the Examiner does not provide an explanation for this suggestion. It is the Applicant's understanding that Streptomyces hyaluronidase will stimulate physiological flow of eye fluids even if there is no aqueous outflow resistance. Further, Yasuyuki et al. only provides for the manufacture of Streptomyces hyaluoronidase and provides no teachings or suggestions on possible uses. The shortcomings of Karageozian are not taught or suggested by Knepper et al. or Yasuyuki et al. Accordingly, the requirement for teaching of all claim limitations is not met.

III. The cited art provides no suggestion or motivation to modify or combine references.

Obviousness can only be established by combining or modifying teachings where there is some teaching, suggestion or motivation to do so found either in the references or in the general knowledge of one of ordinary skill in the art. *In re Fine*, 837 F.2d 1071, 5 U.S.P.Q. 2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 U.S.P.Q. 2d 1941 (Fed. Cir. 1992).

A. Karageozian et al., Knepper et al., and Yasuyuki et al. provide no suggestion or motivation to modify or combine references as a rejection to Claims 1 and 3.

The Examiner uses Knepper et al. to modify Karageozian et al., saying it would have been obvious to one skilled in the art to do so. Applicant respectfully disagrees with this combination. Karageozian et al. is a complete patent for using ovine hyaluronidase to clear hemorrhagic blood from the eye and does not provide suggestion or motivation to use Streptomyces hyaluronidase. The fact that a hyaluronidase from an ovine testicular source can be used to clear hemorrhagic blood does not suggest, and would not be presumed by one skilled in the art, that hyaluronidase from all sources can be utilized for a particular purpose. In fact, in Karageozian et al., the specification clearly states at column 3, lines 39-47, that "[S]ignificant evidence indicates that hyaluronidase enzymes derived from different sources differ in enzyme molecular weight distribution and in specific enzymatic activities. Such variability in molecular weight distribution and specific enzymatic activity are noteworthy considerations in view of the fact that hyaluronidase enzymes may be isolated from a variety of sources, including bovine testes, ovine testes, certain bacteria such as streptomyces, and certain invertebrate animals such as leeches." Karageozian et al. goes on to say at column 4, line 36-38, that the preferred hyaluronidase of Karageozian et al. is obtained from ovine testes.

Further, as discussed previously at page 10, lines 9-23 and page 11, lines 1-10, Knepper et al. only suggests that Streptomyces hyaluronidase decreases aqueous outflow resistance. To Applicant's knowledge, aqueous outflow resistance and clearing of hemorrhagic blood are not related. Accordingly, the disclosure of Knepper et al. would not motivate one skilled in the art to combine Knepper et al. with Karageozian et al. Yasayuki et al. only discloses the production of hyaluronidase from a Streptomyces

source, and therefore provides no suggestion of motivation to combine Karageozian et al. and Knepper to each other or itself.

Based on the above, the cited art does not provide a suggestion or motivation to modify or combine references to achieve the claimed limitations. Therefore, the Examiner has failed to make a prima facie case for obviousness, and this rejection cannot stand.

B. Karageozian, Knepper et al., and Yasuyuki et al, further in view of Straus provide no suggestion or motivation to modify or combine references as a rejection to Claim 5.

The Examiner uses Knepper et al. to modify Karageozian, saying it would have been obvious to one skilled in the art to do so. Karageozian is directed to treating corneal disorders using a hyaluronidase mixture using ovine hyaluronidase, while Knepper is directed to treating aqueous outflow resistance using Streptomyces hyaluronidase. As discussed previously, the Examiner provides no relation or link between treating corneal disorders and aqueous outflow pathway disorders and enhancing spread of local anesthetic the eye; therefore, there is no motivation to combine the teachings of Karageozian and Knepper et al.; therefore there is not motivation to combine these references.

With regards to Straus, the Examiner provides no explanation for modifying Straus using the disclosures of Knepper et al., Karageozian, or Yasuyuki et al., and no suggestion or motivation is provided by the cited references. Straus is directed to a needle for injecting anesthetic into the eye. Straus has no relation to clearing correcting corneal collagen fiber disorganization (the focus of Karageozian), Straus has no relation

to injecting Streptomyces hyaluronidase into the eye to reduce aqueous outflow resistance, and Straus has no relation to the preparation of Streptomyces hyaluronidase. The fact that Straus prefers administering a local anesthetic including hyaluronidase does not suggest or provide motivation to combine the cited references. Each of the cited references contains a complete disclosure totally unrelated the invention of Straus. Further, as discussed above at page 16, lines 8-16, the source of hyaluronidase makes a significant difference in the enzyme activity, and, therefore, the suggestion of hyaluronidase does not suggest Streptomyces hyaluronidase. Thus the rejection of claim 5 should be withdrawn.

C. Karageozian, Knepper et al., and Yasuyuki et al, further in view of Straus provide no suggestion or motivation to modify or combine references as a rejection to Claims 7-9.

The Examiner uses Knepper et al. to modify Karageozian, saying it would have been obvious to one skilled in the art to do so. Applicant asserts that there is no motivation or suggestion to combine these references. Karageozian is directed to treating corneal disorders using a hyaluronidase mixture using ovine hyaluronidase, while Knepper et al. is directed to treating aqueous outflow resistance using Streptomyces hyaluronidase. As discussed previously, the Examiner provides no relation or link between treating corneal disorders and aqueous outflow pathway disorders and stimulating flow of physiological fluids within the eye; therefore, there is no motivation to combine the teachings of Karageozian and Knepper et al. Further, Yasuyuki et al. is directed only to preparation of Streptomyces hyaluronidase, and therefore, provides no such motivation for combination either. Each of the cited references contains a complete

disclosure unrelated to and not suggestive of each other's invention or the present invention. Thus the rejection of claims 7-9 should be withdrawn.

IV. The cited art does not indicate that there is a reasonable expectation of success.

The cited art can be modified or combined to reject claims as prima facie obvious only if there is a reasonable expectation of success. In re Merck & Co., Inc., 800 F.2d 1091, 231 U.S.P.Q. 375 (Fed. Cir. 1986).

A. Karageozian et al., Knepper et al., and Yasuyuki et al. cited against Claims 1 and 3 do not indicate that there is a reasonable expectation of success.

The Examiner provides no explicit reasonable expectation of success of the invention of Claims 1 and 3. However, the Examiner asserts that it would have been obvious to modify Karageozian et al. using Knepper et al. because Knepper et al. decreases aqueous outflow resistance. Applicant asserts that this modification and combination provides no expectation of success.

Karageozian et al. is directed to clearing hemorrhagic blood from the eye using ovine hyaluronidase, and further Karageozian et al. stresses the importance and criticality of hyaluronidase derived from different sources as discussed above at page 16, lines 8-16. Given the fact that different sources provide hyaluronidase with different characteristics and efficacies, Applicant asserts that there would be no reasonable expectation that a modification of Karageozian et al. using Knepper et al. would provide the desired effects of the present invention. Further, given that there is no explained link between clearing of hemorrhagic blood and decreasing aqueous outflow resistance, Applicant asserts that

there would be no reasonable expectation that Streptomyces hyaluronidase would clear hemorrhagic blood just because Knepper et al. indicates that it decreases aqueous outflow resistance. Accordingly, the rejection of claims 1 and 3 must not stand.

B. Karageozian, Knepper et al., and Yasuyuki et al., further in view of Straus cited against Claim 5 do not indicate that there is a reasonable expectation of success.

The Examiner indicates in lines 7-10 of the Advisory Action that "because of the decreased aqueous outflow resistance caused by the Streptomyces Hyaluronidase, one skilled in the art would have expected the Streptomyces Hyaluronidase to also be more effective at spreading local anesthesia through ocular tissue..." Applicant respectfully disagrees with this assertion.

As discussed previously at page 10, lines 9-23 and page 11, lines 1-10, aqueous outflow does not refer to the general flow of all fluids from the eye as suggested by the Examiner. Aqueous outflow resistance is a disorder of the aqueous outflow pathway, and those skilled in the art still do not know the cause of the majority of aqueous humor outflow resistance. The Examiner provides no explanation as to the expectation of success of enhanced spreading of local anesthetic based on decreased aqueous outflow resistance. Applicant asserts that there is no logical connection and no expectation of success.

Claim 5 is directed to applying Streptomyces hyaluronidase to the eye to enhance spreading of local anesthetic. To the knowledge of the Applicant, spreading of local anesthetic into the eye is unrelated to the aqueous outflow pathway and aqueous outflow resistance. Applicant asserts there is no expectation of success based on the disclosure of

Knepper because there is no relation between intraocular injection of Streptomyces hyaluronidase to decrease aqueous outflow resistance and extraocular application of Streptomyces hyaluoronidase to enhance spread of local anesthetic throughout the eye. Accordingly the rejection of claim 5 cannot stand.

C. Karageozian, Knepper et al., and Yasuyuki et al., cited against Claims 7-9 do not indicate that there is a reasonable expectation of success.

The Examiner provides no reasonable expectation of success of combining Karageozian, Knepper et al., and Yasuyuki et al. to provide the invention of Claims 7-9. The Examiner states in lines 7-10 of the Advisory Action that "because of the decreased aqueous outflow resistance caused by the Streptomyces Hyaluronidase, one skilled in the art would have expected the Streptomyces Hyaluronidase to also be more effective at spreading local anesthesia through ocular tissue and to stimulate flow of physiological fluids in the eye." Applicant respectfully disagrees with this assertion.

Karageozian is directed to a method for eliminating corneal collagen fiber disorganization using mixture containing ovine-testicle derived hyaluronidase; Knepper et al. discloses decreasing aqueous outflow resistance using Streptomyces hyaluronidase; and Yasuyuki et al. discloses a method of preparing Streptomyces hyaluronidase. Karageozian does not disclose or suggest that Streptomyces hyaluronidase can be used to stimulate flow of physiological fluid in the eye, but rather discloses that a hyaluronidase mixture reorganizes collagen fibers in the eye. The Examiner does not provide a link between correcting corneal disorders and stimulating flow of fluids in the eye. Further, as discussed in detail above at page 16, lines 8-16, Karageozian stresses in Karageozian et al. that the source of hyaluronidase is critical to hyaluronidase activity. Neither

Knepper et al. nor Yasuyuki et al. provide for using Streptomyces hyaluornidase for stimulating flow of physiological fluid in the eye. Accordingly, Applicant asserts that there is no reasonable expectation of success for stimulating flow of physiological fluid in the eye using Streptomyces hyaluronidase based on the cited references.

V. The cited art teaches away from the claimed invention.

A prima facie case of obviousness can also be rebutted by showing that the art, in any material respect, teaches away from the claimed invention. *In re Geisler*, 116 F.3d 1465, 1471, 43 U.S.P.Q.2d 1362, 1366 (Fed. Cir. 1977).

A. Karageozian et al. and Knepper et al. teach away from the invention of Claims 1 and 3.

Karageozian et al. teaches away from the present invention in that it discloses using hyaluronidase derived from bovine testicles, which is exactly what the present invention is trying to avoid. As discussed above, hyaluronidase from different sources have different enzymatic activities. Accordingly, the use of bovine hyaluronidase to clear hemorrhagic blood from the eye teaches away from using Streptomyces hyaluronidase to clear hemorrhagic blood from the eye.

Thus, the requirement for making a prima facie case of obviousness has not been met. In view of the above, Applicant respectfully requests that the obviousness rejection under 35 U.S.C 103(a) be withdrawn and that Claims 1 and 3 be allowed.

B. Karageozian, Knepper et al., and Yasuyuki et al. in view of Straus teach away from the invention of Claim 5.

Straus teaches away from the present invention in that it discloses injecting a local anesthetic into the eye containing hyaluronidase, while the present invention is directed to applying Streptomyces hyaluronidase to the eye. In fact at column 5, lines 7-10, Straus teaches applying other compounds such as proparacaine HCl to the eye, but specifically discloses the mixture containing hyaluronidase as being injected into the eye. Accordingly, Straus teaches away from applying Streptomyces hyaluronidase to the eye to enhance spreading of local anesthetic. Thus the reaquirement for making a prima facie case of obviouness has not been met, and Applicant respectfully requests that the rejection of claim 5 be withdrawn.

C. Karageozian, Knepper et al., and Yasuyuki et al. teach away from the invention of Claims 7-9.

Karageozian teaches away from the present invention in that it discloses using hyaluronidase derived from ovine testicles, which is exactly what the present invention is trying to avoid. As discussed above, Inventor Karageozian points out that hyaluronidase from different sources have different enzymatic activities. Accordingly, the use of ovine hyaluronidase to stimulate flow of physiological fluids in the eye teaches away from using Streptomyces hyaluronidase to stimulate flow of physiological fluids in the eye.

Further Knepper et al. teaches away from the present invention in that it discloses correcting the aqueous outflow pathway to relieve pressure in the eye. In contrast, the present invention discloses stimulating flow of physiological fluids in the eye independent of the aqueous outflow pathway. For example, applying Streptomyces hyaluornidase to the eye stimulates fluid flow so as to not only treat glaucoma (an effect

of aqueous outflow resistance) but also to treat thrombosis, detached retina, and obstruction removal.

Thus, the requirement for making a prima facie case of obviousness has not been met. In view of the above, Applicant respectfully requests that the obviousness rejection under 35 U.S.C 103(a) be withdrawn and that Claims 7-9 be allowed.

SUMMARY

Applicants assert that the claimed invention is in condition for allowance and respectfully request that the rejection of claims 1, 3, 5, and 7-9 be withdrawn. Notification to this respect is respectfully requested.

Any deficiency in fees due in relation to the timely filing of this Appeal Brief are hereby authorized to be deducted from Deposit Account No. 16-0478.

Respectfully submitted,

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By: Kimberly Q. Snead
Kimberly Q. Snead
Reg. No. 45,119

Parker & DeStefano
300 Preston Avenue
Suite 300
Charlottesville, VA 22902
Telephone: 434-817-6606
Facsimile: 434-817-6610

APPENDIX A—Listing of Pending Claims

Claim 1: A method for accelerating the clearance of hemorrhagic blood from the vitreous humor of a mammalian eye, comprising the step of injecting into the vitreous humor a solution which contains hyaluronidase from *Streptomyces hyalurolyticus* to provide a dose having a hyaluronidase activity of at least about 10 Turbidity Reducing Units (TRU) of said hyaluronidase, said solution being essentially free of contaminating protease.

Claim 2 (canceled)

Claim 3: A method of treating eye disorders comprising the step of applying essentially protease-free hyaluronidase from *Streptomyces hyalurolyticus* to the eye, wherein said hyaluronidase is dissolved in a saline solution, and wherein said treating of said eye disorders is the clearing of hemorrhagic blood from the vitreous humor of a mammalian eye using an amount of hyaluronidase sufficient to clear the blood.

Claim 4: A method of treating eye disorders comprising the step of applying essentially protease-free hyaluronidase from *Streptomyces hyalurolyticus* to the eye, wherein said hyaluronidase is dissolved in a saline solution, and wherein said treating of an eye disorder is the softening the cornea of a mammalian eye prior to refractive correction by using an amount of hyaluronidase sufficient to soften the cornea.

Claim 5: A method of treating eye disorders comprising the step of applying essentially protease-free hyaluronidase from *Streptomyces hyalurolyticus* to the eye, wherein said hyaluronidase is dissolved in a saline solution, and wherein said treating of an eye disorder is the spreading local anesthesia more effectively through ocular tissue

prior to surgical interventions by using an amount of hyaluronidase sufficient to spread anesthesia.

Claim 6: A method of treating eye disorders comprising the step of applying essentially protease-free hyaluronidase from *Streptomyces hyalurolyticus* to the eye, wherein said hyaluronidase is dissolved in a saline solution, and wherein said treating of an eye disorder is the isolating of collagen to produce contact lenses by using hyaluronidase from *Streptomyces hyalurolyticus*.

Claim 7: A method of treating eye disorders comprising the step of applying essentially protease-free hyaluronidase from *Streptomyces hyalurolyticus* to the eye, wherein said hyaluronidase is dissolved in a saline solution, and wherein said treating of an eye disorder is the stimulating of flow of physiological fluids in the eye which comprises contacting a physiological fluid of the eye with ~~a~~ said hyaluroinidase using an amount of ~~the~~ hyaluronidase sufficient to stimulate the flow of said fluid.

Claim 8: The method of claim 7 wherein the physiological fluid in the eye is contacted for the treatment of glaucoma, thrombosis, detached or impending detached retina, or for the non-surgical removal of obstructions.

Claim 9: The method of claim 1, wherein said hyaluronidase activity is in the range of about 100-300 Turbidity Reducing Units (TRU) of said hyaluronidase.